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Prognostic Value of Cardiac Computed Tomography Angiography

A Systematic Review and Meta-Analysis

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Objectives The purpose of this study was to systematically review and perform a meta-analysis of the ability of cardiac computed tomography angiography (CCTA) to predict future cardiovascular events and death.

Background The diagnostic accuracy of CCTA is well reported. The prognostic value of CCTA has been described in several studies, but many were underpowered. Pooling outcomes increases the power to predict rare events.

Methods We searched multiple databases for longitudinal studies of CCTA with at least 3 months follow-up of symptomatic patients with suspected coronary artery disease (CAD) reporting major adverse cardiovascular events (MACE), consisting of death, myocardial infarction (MI), and revascularization. Annualized event rates were pooled using a bivariate mixed-effects binomial regression model to calculate summary likelihood ratios and receiver-operating characteristic curves.

Results Eighteen studies evaluated 9,592 patients with a median follow-up of 20 months. The pooled annualized event rate for obstructive (any vessel with >50% luminal stenosis) versus normal CCTA was 8.8% versus 0.17% per year for MACE ($p < 0.05$) and 3.2% versus 0.15% for death or MI ($p < 0.05$). The pooled negative likelihood ratio for MACE after normal CCTA findings was 0.008 (95% confidence interval [CI]: 0.0004 to 0.17, $p < 0.001$), the positive likelihood ratio was 1.70 (95% CI: 1.42 to 2.02, $p < 0.001$), sensitivity was 0.99 (95% CI: 0.93 to 1.00, $p < 0.001$), and specificity was 0.41 (95% CI: 0.31 to 0.52, $p < 0.001$). Stratifying by no CAD, nonobstructive CAD (worst stenosis <50%), or obstructive CAD, there were incrementally increasing adverse events.

Conclusions Adverse cardiovascular events among patients with normal findings on CCTA are rare. There are incrementally increasing future MACE with increasing CAD by CCTA. (J Am Coll Cardiol 2011;57:1237–47) © 2011 by the American College of Cardiology Foundation

Since the first report of the use of contrast-enhanced computed tomography (CT) to obtain noninvasive coronary angiograms in 1995 (1), cardiac computed tomography angiography (CCTA) has evolved to become a highly accurate method in the diagnosis of coronary artery disease (CAD), comparable to conventional invasive coronary angiography (2). As a result, modern CCTA has been rapidly adopted clinically for the assessment of symptomatic patients with suspected CAD. Currently, scientific guidelines exist for the appropriate use (3), performance (4), and interpretation (5) of CCTA. Despite the current widespread use of CCTA, its prognostic ability is not well defined.

The prognostic value of coronary calcification by CT has been well described (6), but the ability of CCTA to predict future clinical outcomes is less well established. The prognostic value of normal CCTA has been reported in several studies, but with varying outcomes (7–30). Some of these studies were not adequately powered to detect differences in rates of clinical outcomes such as death, myocardial infarction (MI), and coronary revascularization. A systematic review from 2008 reported on the diagnostic accuracy, cost-effectiveness, and prognostic value of CCTA, but the prognostic assessment was limited by only 3 papers having been reported, 2 in abstract format, at the time of analysis (2). Several subsequent studies have been published in the interim. A recent CCTA expert consensus statement sponsored by the American College of Cardiology and 6 additional medical societies points to the need for continued

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Abbreviations and Acronyms

CAD = coronary artery disease

CCTA = cardiac computed tomography angiography

CI = confidence interval

CT = computed tomography

EBCT = electron beam computed tomography

−LR = negative likelihood ratio

+LR = positive likelihood ratio

MACE = major adverse cardiovascular event(s)

MDCT = multidetector computed tomography

MI = myocardial infarction

collection and assessment of prognostic data after CCTA (31,32).

Therefore, we undertook a systematic review and meta-analysis of the available published literature to investigate the prognostic value of normal CCTA for major adverse cardiovascular events (MACE), death, MI, or coronary revascularization.

Methods

Data sources. We searched MEDLINE, Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews and Effects, Cochrane Methodology Register, Health Technology Assessment database, National Health Service Economic Evaluation Database, Embase, and the Cochrane Controlled Trials Register for studies published from January 1, 1995 through March 9, 2010. We used the text words and related Medical Subject Headings (MeSH) for cardiac, CT, angiography, prognosis, death, myocardial infarction, and survival. There were no language restrictions. Search results were limited to adults. References of reviewed articles were also searched for relevant titles. Our PubMed search query was (computed tomography or CT) AND (prognosis OR death OR mortality OR myocardial infarction OR survival) AND (cardiac or coronary) AND angiography AND (Humans-[Mesh] AND adult[MeSH] AND ("1995/01/01"[PDAT] : "2010/03/09"[PDAT]). We executed and reported our findings according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (33–35).

Study selection. Two investigators (1 physician and 1 physician/epidemiologist) independently conducted the literature search and extraction of relevant titles. The title and abstract of potentially relevant studies and review articles were screened for appropriateness before retrieval of the full article, where relevant. We included diagnostic studies of CCTA with at least 3 months of follow-up for symptomatic patients with known or suspected CAD reporting MACE, death, MI, and coronary revascularization. We included retrospective and prospective observational studies. We sought to evaluate CCTA in a population consistent with its current appropriate use (patients with symptoms of suspected CAD); therefore, we did not include studies of patient populations characterized as asymptomatic screening, pre-operative risk stratification, or routine follow-up coronary artery bypass grafts or percutaneous intervention. We excluded diagnostic accuracy studies without clinical outcomes.

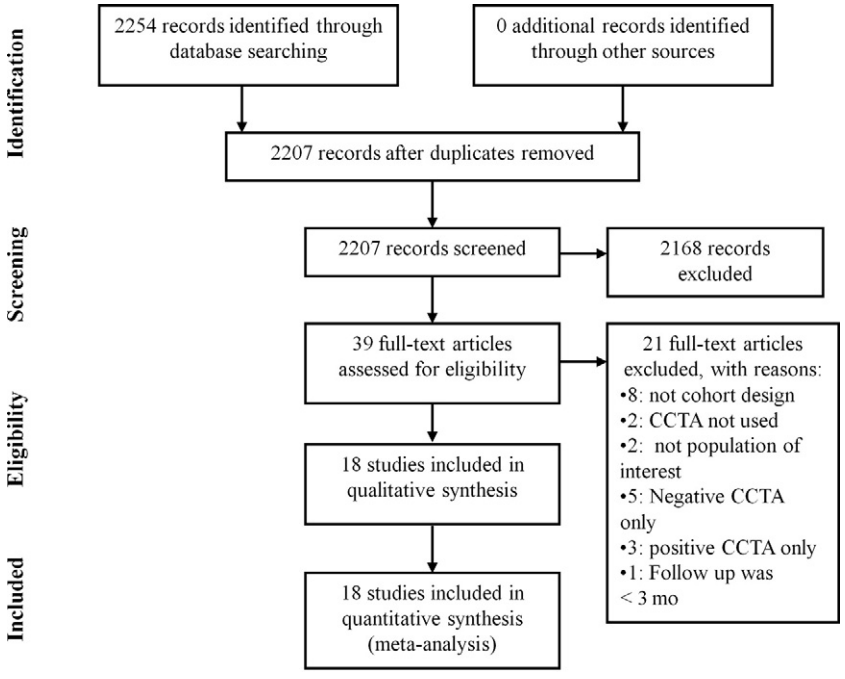

Figure 1 Literature Search Results

Eighteen studies met criteria for inclusion. CCTA = cardiac computed tomography angiography.

Table 1 18 Studies Included in Meta-Analysis of CCTA Prognosis

First Author (Ref. #)	Year	Design	Population Known or Suspected CAD	Scanner	n	Follow-Up (Months)	Age (yrs)	% Male	Quality Sel/Comp/Ou–Total
Gopal et al. (12)	2009	PCO	Known or suspected	EBCT	454	40	58	70	4/2/3–9
Ostrom et al. (18)	2008	RetCO	Suspected	EBCT	2,538	78	59	70	4/2/3–9
Min et al. (16)	2007	PCO	Suspected	16-slice	1,127	15	62	43	4/2/3–9
Noda et al. (17)	2008	PCO	Suspected	16-slice	30	10	65	43	3/0/1–4
Pundziute et al. (20)	2007	PCO	Known or suspected	16-slice	100	13	59	73	3/2/3–8
Shaw et al. (21)	2008	PCO	Suspected	16-slice	693	16	62	52	4/2/3–9
Abidov et al. (29)	2009	PCO	Suspected	64-slice	199	28	54	54	4/2/3–9
Aldrovandi et al. (26)	2009	PCO	Suspected	64-slice	187	24	63	64	4/2/3–9
Barros et al. (27)	2009	RetCO	Suspected	64-slice	31	21	58	70	3/0/3–6
Cademartiri et al. (7)	2008	PCO	Known or suspected	64-slice	98	20	67	32	3/2/3–8
Carrigan et al. (8)	2009	RetCO	Suspected	64-slice	227	28	54	61	4/2/3–9
Chow et al. (24)	2010	PCO	Suspected	64-slice	2,076	17	58	52	4/2/3–9
Danciu et al. (28)	2007	PCO	Suspected	64-slice	421	15	64	63	3/0/3–6
Fazel et al. (10)	2009	RetCO	Suspected	64-slice	436	36	55	45	4/0/3–7
Gaemperli et al. (11)	2008	PCO	Known or suspected	64-slice	220	14	63	65	3/2/3–8
Hay et al. (30)	2009	RetCO	Suspected	64-slice	138	20	57	73	3/0/3–9
Rubinshtein et al. (19)	2006	RetCO	Suspected	64-slice	100	12	56	57	4/2/3–9
van Werkhoven et al. (22)	2009	PCO	Suspected	64-slice	517	22	59	59	3/2/3–8
SUM					9,592	429			
Mean/median					224	20	59	58	8

CAD = coronary artery disease; Comp = comparison; Ou = outcome; PCO = prospective cohort; RetCO = retrospective cohort; Sel = selection.

Data abstraction and validity assessment. Two investigators (1 physician and 1 physician/epidemiologist) independently abstracted data using a standardized form. We extracted the following demographic data: author, year of publication, design, follow-up duration, sample size, type of CT scanner (electron beam computed tomography [EBCT], 16-slice multidetector computed tomography [MDCT] angiography, 64-slice MDCT angiography), age, known or suspected CAD, and percentage of male sex. Clinical outcomes included the raw data for the combined outcome of MACE (all-cause mortality, nonfatal MI, revascularization, and re-admission for unstable angina) and the independent outcomes of all-cause mortality, cardiovascular mortality, nonfatal MI, and revascularization. When

Table 2 Adverse Cardiovascular Events by Study and CCTA Result

	No CAD					Nonobstructive CAD					Obstructive CAD				
First Author (Ref. #)	n	MACE	Death	MI	Revasc	n	MACE	Death	MI	Revasc	n	MACE	Death	MI	Revasc
Gopal et al. (12)	157	0	0	0	0	204	0	0	0	0	93	40	0	20	20
Ostrom et al. (18)	1,085	18	18			1,060	36	36			393	32	32		
Min et al. (16)	333	1	1			157	9	9			637	28	28		
Noda et al. (17)	12	0	0	0	0										
Pundziute et al. (20)	20	0	0	0	0	48	6				32	20			
Shaw et al. (21)	303	1	1			39	1	1			351	21	21		
Abidov et al. (29)	93	0	0	0	0	70	3	0	0	3	36	15	0	0	15
Aldrovandi et al. (26)	65	0	0	0	0	87	3	1	0	3	35	17	0	3	13
Barros et al. (27)	6	0	0	0	0	18	1	1	0	0	7	4	0	0	4
Cademartiri et al. (7)	23	0	0	0		49	0	0			26	6	0	3	
Carrigan et al. (8)	96	0	0	0	0	76	2	0	1	1	55	16	1	2	13
Chow et al. (24)	591	0	0	0		866	13	8	5		619	35	17	18	
Danciu et al. (28)	87	0	0	0	0	150	6	0	0	1	184	55	1	1	53
Fazel et al. (10)	376	0	0	0	0										
Gaemperli et al. (11)	43	1	1	0	0	82	3	2	1	3	95	56	1	2	55
Hay et al. (30)	59	0	0	0	0	57	0	0	0	0	22	8	0	0	8
Rubinshtein et al. (19)	53	0	0	0	0	18	3	0	0	3	29	18	0	0	18
van Werkhoven et al. (22)	155	2				204	4				158	10			
SUM	3,557	23	21	0	0	3,185	90	58	7	14	2,772	381	101	49	199
% Annual event rate		0.17	0.15	0.00	0.00		1.41	0.74	0.30	1.25		8.84	2.22	2.12	24.82

CAD = coronary artery disease; MACE = major adverse cardiac event(s); MI = myocardial infarction; Revasc = revascularization.

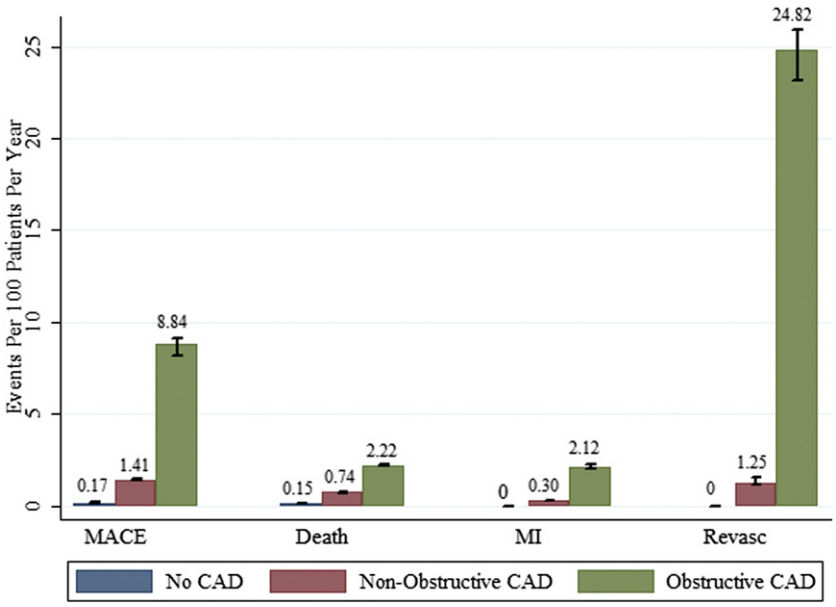

Figure 2 **Annual Event Rates Stratified by Cardiac Computed Tomography Angiography Result**

Percentage of annualized event rates for combined major adverse cardiac events (MACE), death (all-cause), myocardial infarction (MI), and revascularization (Revasc), stratified by cardiac computed tomography angiography diagnosis of no coronary artery disease (CAD), nonobstructive CAD (<50% stenosis), and obstructive CAD (>50% stenosis). All groups were significantly different by analysis of variance ($p < 0.05$).

disagreements occurred among data extractors, the final decision was made by consensus of all authors.

Quality assessment. Two reviewers independently rated study quality using the Newcastle-Ottawa Scale for the assessment of quality of observational studies. This instrument is recommended for use by the Cochrane Collaborative Group for the assessment of quality of nonrandomized studies (36). Assessment of quality is graded by the description of patient selection (4 criteria), study-control group comparability (1 criterion), and outcome assessment. Based on previous recommendations, studies meeting ≥5 criteria were considered to be high quality (36).

Data synthesis. Raw data for dichotomous event outcomes were converted to annualized event rates and then pooled using a bivariate mixed-effects binomial regression model, using the "metandi" module in Stata (version 11.0 Special Edition, StataCorp, College Station, Texas) (37). This model was used due to frequent zero cells that occurred because most patients with normal CCTA findings do not have cardiac events, and hard events were not common even among patients with abnormal scans. We then calculated summary sensitivity, specificity, likelihood ratios, diagnostic odds ratios, a Fagan's nomogram (38), and summary receiver-operating characteristic curves. As a sensitivity analysis to test the validity of annualized event rates, we also evaluated the dataset using absolute events for the 2 × 2 table for each study in the same binomial regression model.

The primary outcome was the negative likelihood ratio (−LR) of MACE (death, MI, unstable angina, or revascularization) after normal findings on CCTA. Secondary outcomes included −LR of death, MI, and revascularization in addition to the sensitivity of CCTA to diagnose patients for the risk of these future events. Our design focused on sensitivity and −LR because these are the clinical parameters of interest for CCTA, which is used to rule out CAD in symptomatic at-risk patients. We evaluated specificity and the positive likelihood ratio (+LR), although these values are of lesser clinical utility for CCTA, which is not a confirmatory test of future clinical events. Stratified analysis was performed to evaluate for influence of the covariates age, sex, type of CT scanner, population studied (known or suspected vs. suspected CAD), and study quality. We defined a normal (or negative) CCTA study as no, minimal, or no significant CAD as reported in each paper. Nonobstructive CAD was defined as worst stenosis (by coronary lumen diameter of any coronary artery) of <50% and obstructive CAD as >50% coronary lumen diameter stenosis by CCTA of any coronary artery.

Methods to explore heterogeneity within systematic reviews of diagnostic studies are less well established than for randomized trials (39). The metandi module allows for assessment of heterogeneity through summary statistic variability and graphically with Galbraith plots (36). Additionally, we conducted a sensitivity analysis of all summary estimates using a fixed-effects model with calculation of the I^2 statistic. The I^2 statistic provides an estimate of the amount of variance due to heterogeneity rather than chance and is based on the traditional measure of variance, the Cochrane Q statistic. When hetero-

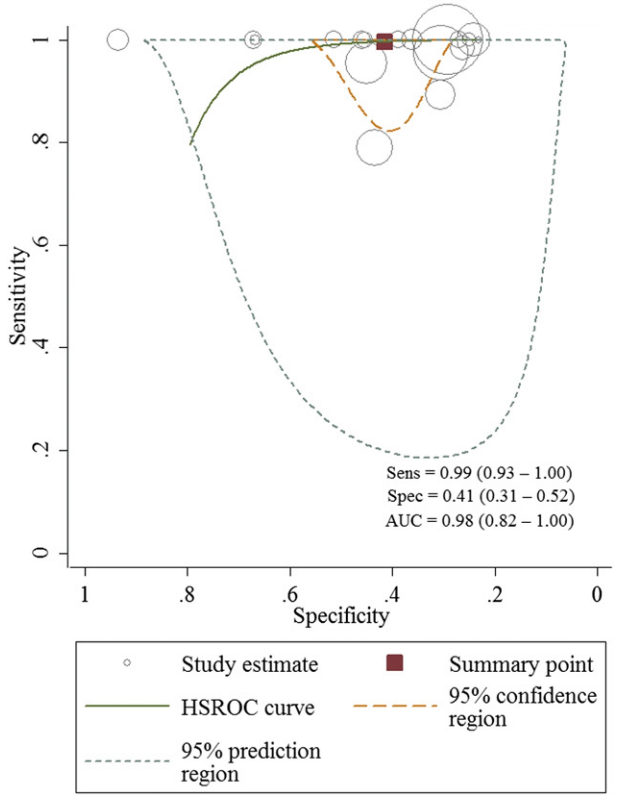

Figure 3 **HSROC Curve for Prediction of Future MACE by CCTA**

Hierarchical summary receiver-operating characteristic (HSROC) curve for the diagnostic performance of cardiac computed tomography angiography to discriminate those with no coronary artery disease (CAD) from those with any evidence of CAD for the prediction of combined major adverse cardiac events, including all-cause mortality, myocardial infarction, and revascularization. The **size of the circles** indicates the weight of each study. AUC = area under the curve; Sens = sensitivity; Spec = specificity.

geneity is significant, stratified analyses are conducted to assess for potential confounders' contribution to heterogeneity, including age, sex, type of scanner, follow-up duration, quality of study, clinical outcomes reported, and population studied (known or suspected vs. suspected CAD). To exclude the possibility that any one study was exerting excessive influence on the results, we conducted a sensitivity analysis by systematically excluding each study at a time and then rerunning the analysis to assess the change in effect size. Publication bias was assessed using the method of Deeks et al. (40). This method is preferred over conventional tests more commonly used for randomized trial meta-analyses because these tests of publication bias or small study effects are less reliable for diagnostic studies (40). The meta-analysis was performed with Stata (version 11.0, StataCorp). To compare the mean annualized event rates among the 3 CCTA outcomes (no CAD, nonobstructive CAD, and obstructive CAD), analysis of variance was performed using SPSS software (version 13.0, SPSS Inc., Chicago, Illinois). Outliers were defined during sensitivity analysis as individual outcomes >2 SDs from the pooled outcome. All p values were 2-tailed and with an alpha of 0.05.

Results

Literature search. The initial search yielded 2,254 references. We eliminated 2,215 after initial screening. The abstract or full text of the 39 remaining studies were evaluated to determine eligibility. Twenty-one studies (14,15,23,25,28,41–56) were excluded after further review for reasons outlined in Figure 1. Eighteen studies were identified for inclusion from the literature search (7,8,10–12,16–22,24,26–30). No additional studies were identified from the references of these articles. Two authors were contacted for additional information. Both authors replied; however, the studies lacked data on normal CAD outcomes and were excluded (42,57).

Characteristics of the included studies. Table 1 presents the demographic data for the 18 included studies. There were 9,592 patients (6,035 positive CCTA findings and 3,557 normal CCTA findings) included with a median follow-up of 20 months. The mean age was 59 ± 2 years, and the patients were 58 ± 10% male (range 32% to 73%). All studies followed a cohort of patients with symptoms suspected to be attributable to CAD, evaluated with CCTA. Fourteen studies excluded patients with previously diagnosed CAD (suspected CAD only). Four of the studies included patients with known CAD who were undergoing new evaluation for possible ischemic chest pain symptoms. One study was rated low quality, and the other 17 of the included studies were rated good quality (Table 1). Raters agreed 100% on categorical study quality (poor vs. acceptable, kappa = 1.00). There was 95% per-point agreement on each item per study of the Newcastle-Ottawa Scale (overall kappa = 0.77, $p < 0.001$).

Annualized event rates. Table 2 presents the clinical outcomes by study and CCTA findings. MACE occurred at an absolute rate in 0.6% of patients with negative scans and death or MI in 0.6% (all events were due to all-cause mortality). There were no coronary revascularizations, MIs, or admissions to the hospital for unstable angina among those with normal findings on CCTA. Cardiovascular mortality was not able to be specified in most papers because the method of assessing mortality was most often by the Social Security Death Index (16,21,22,24). Chow et al. (24) noted that the 1 death in their no CAD group was malignancy related. MACE occurred in 8.2% of patients with positive scans, and death or MI occurred in 3.7%. The weighted average annualized MACE rate for positive versus negative CCTA findings was 8.8% (predominantly revascularization) versus 0.17% per year ($p < 0.05$). For death or MI, the weighted average annualized event rate was 3.2% versus 0.15% ($p < 0.05$) for positive versus negative scans. After stratifying by no CAD, nonobstructive

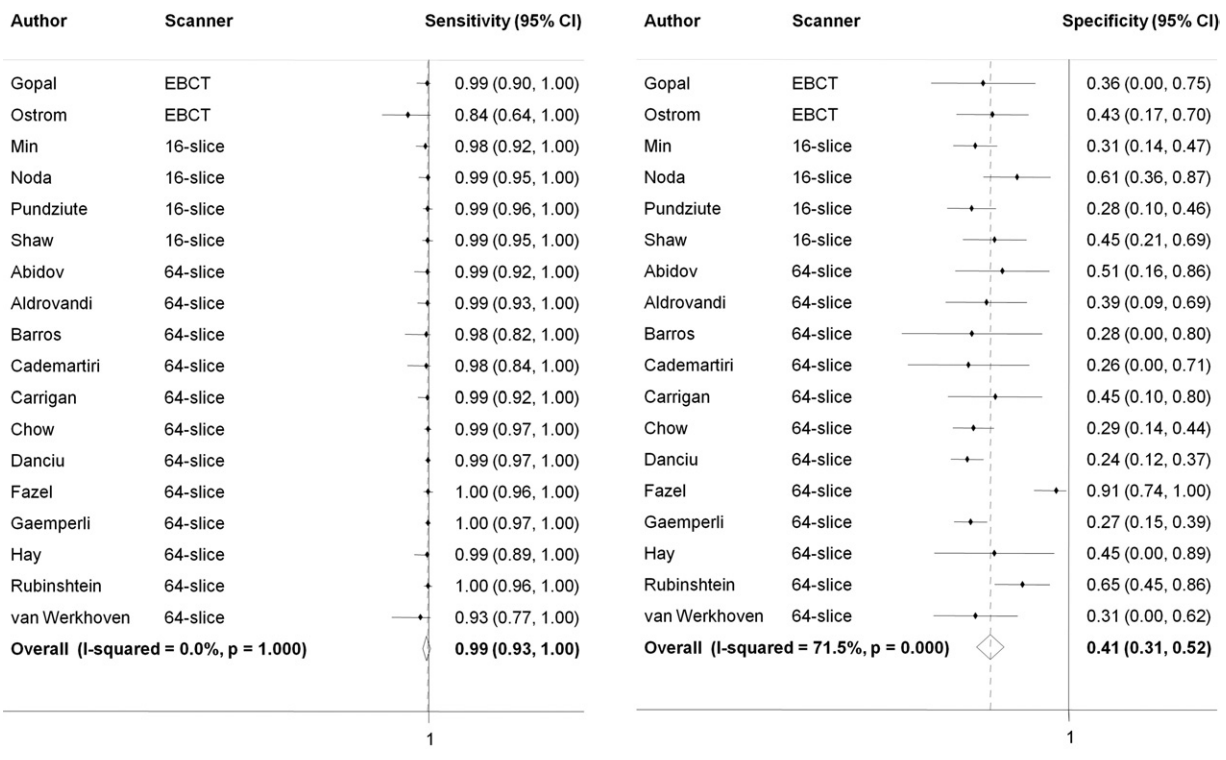

Figure 4 **Pooled Sensitivity and Specificity for Future MACE Using a Bivariate Mixed-Effects Binomial Regression Model**

Sensitivity was homogeneous across this outcome and other subgroups. Specificity was heterogeneous.
CI = confidence interval; EBCT = electron beam computed tomography; MACE = major adverse cardiac event(s).

CAD, and obstructive CAD, incrementally increasing event rates were noted, as depicted in Figure 2.

Test parameters and likelihood ratios. Figure 3 depicts by summary of the receiver-operating characteristic curve the test parameters for performance of CCTA to predict future MACE among those with any CAD versus those without any CAD by CCTA. Figure 4 demonstrates the pooled sensitivity and specificity for MACE by any CAD versus no CAD. The specificity was heterogeneous in all subgroups. Figure 5 summarizes the likelihood ratios for CCTA diagnosis of no CAD versus nonobstructive CAD versus obstructive CAD, stratified by MACE, death, and death or MI. The pooled −LR for MACE in patients with negative findings on CCTA was 0.008 (95% confidence interval [CI]: 0.003 to 0.21, $p < 0.001$, $I^2 = 0\%$); +LR 1.70 (95% CI: 1.42 to 2.02, $p < 0.001$, $I^2 = 87\%$), sensitivity 0.99 (95% CI: 0.93 to 1.00, $p < 0.001$, $I^2 = 0\%$), and specificity 0.41 (95% CI: 0.31 to 0.52, $p < 0.001$, $I^2 = 72\%$). Figure 6 depicts how a −LR and +LR affect post-test probability after CCTA for a hypothetical patient with a 20% pre-test probability of having future MACE.

Sensitivity analysis. There was no significant heterogeneity by I^2 for MACE, death, MI, or revascularization when comparing the −LR by any of the outcomes among the subgroups any CAD versus no CAD and no CAD versus nonobstructive CAD. Two outlier studies were identified for obstructive versus nonobstructive CAD by MACE (Min et al. [16] and Ostrom et al. [18]) (Fig. 7). For this small subgroup, only these studies were excluded from the final quantified analysis.

There was no evidence of publication bias by the Deeks et al. (40) test ($p = 0.10$). Stratified analysis showed that the effect size was not dependent on sex, patient population (suspected or known/suspected CAD), or quality of study. Duration of follow-up and type of scanner were significantly related to effect size. The sensitivity analysis demonstrated that 78% of the MACE in the no CAD group occurred in the paper by Ostrom et al. (18). This paper was also an outlier in terms of duration of follow-up (78 months). However, outcomes did not significantly differ after excluding the Ostrom et al. (18) study (−LR = 0.0099; 95% CI: 0.002 to 0.59; $p < 0.001$). A comparison of the sensitivity to rule out CAD associated with future adverse events by type of scanner was underpowered due to the few studies in each stratum. Evaluation of revascularization rates by scanner type was underpowered because only 2 studies of 16-slice scanners and 1 EBCT angiography study reported revascularization. For studies that used only 64-slice MDCT, the sensitivity to predict MACE was 99.9% (95% CI: 0.58 to 1.00; $p < 0.001$). For those that used 16-slice MDCT angiography or EBCT angiography, sensitivity to predict MACE was 98% (95% CI: 0.81 to 1.00; $p < 0.001$).

Sensitivity analyses conducted to test the validity of pooled annualized event rates compared the annualized event rates to an analysis performed with absolute counts for respective 2 × 2 tables. The latter method produced similar effect sizes, but was limited by an inability to estimate a logistic model for several subgroups and significant heterogeneity. For example, for the pooled MACE using absolute rates for any CAD versus no CAD, the −LR was 0.02 (95% CI: 0.00 to 0.11; $p < 0.001$; $I^2 = 81\%$), the +LR was 1.70 (95% CI: 1.4 to 2.1; $p < 0.001$, $I^2 = 95\%$), sensitivity was 0.99 (95% CI:, 0.96 to 1.00; $p < 0.001$; $I^2 = 83\%$), and specificity was 0.41 (95% CI: 0.31 to 0.53; $p < 0.001$; $I^2 = 98\%$). Use of annualized event rates was more homogeneous.

Discussion

Although the diagnostic accuracy of CCTA has been reported in >50 studies and meta-analyses (58,59), the prognostic value of CCTA for predicting clinical events is less defined. Our systematic review and meta-analysis is the first comprehensive analysis of multiple recent longitudinal studies describing the prognostic value of CCTA (7–25). We have shown that the absence of CAD on CCTA conveys an excellent prognosis for symptomatic patients being evaluated for suspected CAD. The low annual event rate for those with normal CCTA findings is comparable to the background event rate among healthy low-risk individuals (<1%) (60). In addition, the low event rate for normal findings on CCTA of 0.16% is comparable to the event rate reported in a previous meta-analysis of patients with normal findings on other noninvasive risk stratification modalities, such as stress echocardiography (0.45%) and myocardial perfusion scan (0.54%) (61). There were no definite CAD-specific events in the group with normal CCTA findings (all 23 events were all-cause mortality) over a median follow-up of 20 months (maximum 78 months). As shown in Figures 3, 4, and 5, CCTA has excellent sensitivity (99%) and −LR (0.008) to exclude future coronary clinical events when pooled across the 9,592 patients with symptoms of possible angina in these 17 studies over a median 20-month follow-up duration.

Where CCTA findings were abnormal, we found incrementally increasing cardiovascular events (MI and revascularization) and all-cause mortality rates with increasing severity of CAD (Fig. 2). For patients with nonobstructive disease, the event rates are higher than those without disease. A marked increase in events (including death) is seen for those with obstructive CAD (at least 1 lesion with >50% stenosis). The increase in events seen between groups stratified by CAD severity was also consistent among each of the components of the primary outcome variable (MACE): death, MI, and coronary revascularization. Therefore, the concept that CCTA offers anatomic but not prognostic value compared with widely used functional stress testing is no longer accurate.

However, although adverse events are rare among patients with normal CCTA findings, a positive scan is not strongly predictive of future MACE. This is because many patients with CAD do not have events when followed over 20 months (the annualized MACE incidence was only 8.8%; thus, the majority of patients even with disease do not have outcomes). Specificity and +LR are less clinically

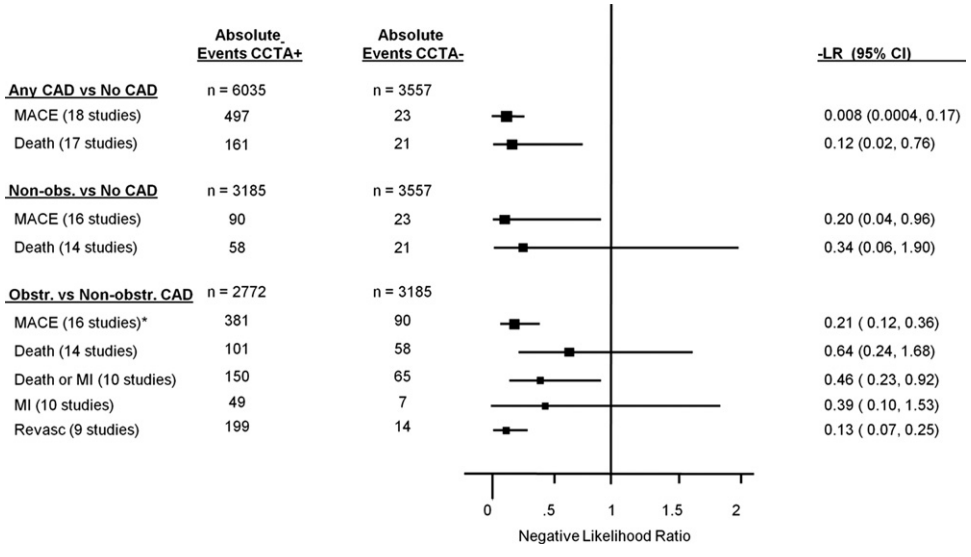

Figure 5 Pooled −LR for Future MACE, Death, Death or MI, MI, and Revascularization Stratified by CCTA Findings

Absolute event rates are displayed. Likelihood ratios were pooled by annualized event rates using a bivariate mixed-effects binomial regression model to calculate test parameters and summary receiver-operating characteristic curves. There were no MI or revascularization events in the no CAD group; therefore, no likelihood ratio is calculated for those comparisons. *Two heterogeneous studies (Min et al. [16] and Ostrom et al. [18]) removed from this end point. −LR = negative likelihood ratio; other abbreviations as in Figures 1, 2, and 4.

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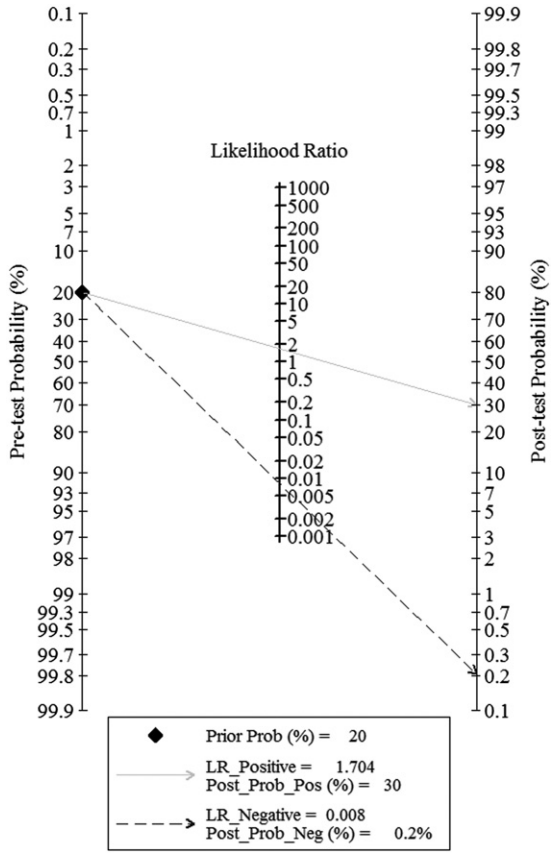

Figure 6 **Fagan's Nomogram for Prediction of Future MACE by CCTA**

Fagan's nomogram for the prediction of future major adverse cardiac events by cardiac computed tomography angiography (CCTA) for a hypothetical patient with a 20% pre-test probability of disease, comparing CCTA positive findings (any coronary artery disease [CAD]) with CCTA negative findings (no CAD). LR_Negative = negative likelihood ratio; LR_Positive = positive likelihood ratio; Post_Prob_Neg = negative post-test probability; Post_Prob_Pos = positive post-test probability.

meaningful when used in this setting, and we focused a priori on −LR and sensitivity because CCTA is a rule-out test, as demonstrated in Figure 6. Furthermore, the specificity and +LR are heterogeneous in this setting, although this is expected because most meta-analyses of diagnostic tests have at least 1 heterogeneous test parameter and the specificity of CCTA for prediction of future MACE is anticipated to vary by characteristics of the study population such as age and pre-existing disease, although available subgroups to analyze for these effects were small in this meta-analysis.

There are several additional important considerations in viewing this information. First, the authors of many of the earlier studies included in this analysis reported prognosis based on a relatively simple classification of CAD luminal stenosis, specifically, no CAD, nonobstructive CAD, or potentially obstructive CAD (>50% stenosis). Although some studies defined normal findings on CCTA as the absence of disease and some allowed for no or minimal disease, this type of stratification has value and is informative clinically. For example, the presence or absence of potentially obstructive CAD is typically the main clinical question being sought by providers referring symptomatic patients for CCTA. However, more precise measurements of overall CAD burden, such as the number of vessels or coronary segments involved or with stenosis, location (e.g., left main or proximal left anterior descending artery involvement), number of vessels with severe stenosis (>70%), and potentially overall plaque volume or plaque scores have been shown to provide refinement of patient prognosis (16,21,24). In addition to lumen stenosis, other plaque characteristics, such as individual plaque volume, the presence and degree of coronary artery positive remodeling (expansion), plaque calcification characteristics, and the presence of very low density plaque, may also influence prognosis and require further study (13,15,62).

This analysis included studies using different generations of CT scanning technology. For example, 2 studies were included that used EBCT, and 4 were conducted with 16-slice MDCT scanners, a technology since surpassed by even more modern (64-, 256-, and 320-slice and dual-source) MDCT scanners, which have higher spatial resolution and overall improved image quality. The results demonstrating a very good prognosis in the absence of CAD and an incremental increase in annual MACE rates with increasing degrees of coronary artery stenosis were consistent when stratified by scanner type, although there is known to be increasing angiographic accuracy with newer generations of CCTA (63,64). However, this meta-analysis was not powered to detect differences in prognostic value comparatively by each scanner subtype because there were only 2 studies using EBCT, 4 using 16-slice MDCT, and the remainder using 64-slice MDCT. All scanner types had good test parameters for ruling out future CAD outcomes (Fig. 4). However, most events among patients with normal CCTA findings (18 all-cause deaths) occurred in the Ostrom et al. study with EBCT angiography, resulting in decreased sensitivity (due to increased false negatives) for that study of 0.84 (95% CI: 0.64 to 1.00) (Fig. 4).

Although our study was not limited by significant statistical heterogeneity for almost all end points' sensitivity and −LR (except for 2 outlier studies for the MACE outcome for obstructive CAD vs. nonobstructive CAD), we evaluated for trends among subgroups with stratified analyses and metaregression in this subgroup. We also examined the heterogeneity within the specificity and +LR. However, significant heterogeneity among at least 1 test parameter in meta-analyses of diagnostic studies is a frequently reported occurrence (65). Evaluation of heterogeneity for reviews of diagnostic studies is less robust than for randomized studies, but we used Galbraith plots to inspect for outliers and influential studies, stratified analyses, and metaregression. Stratified analyses showed no significant impact of baseline sex, age, whether the study included patients with estab-

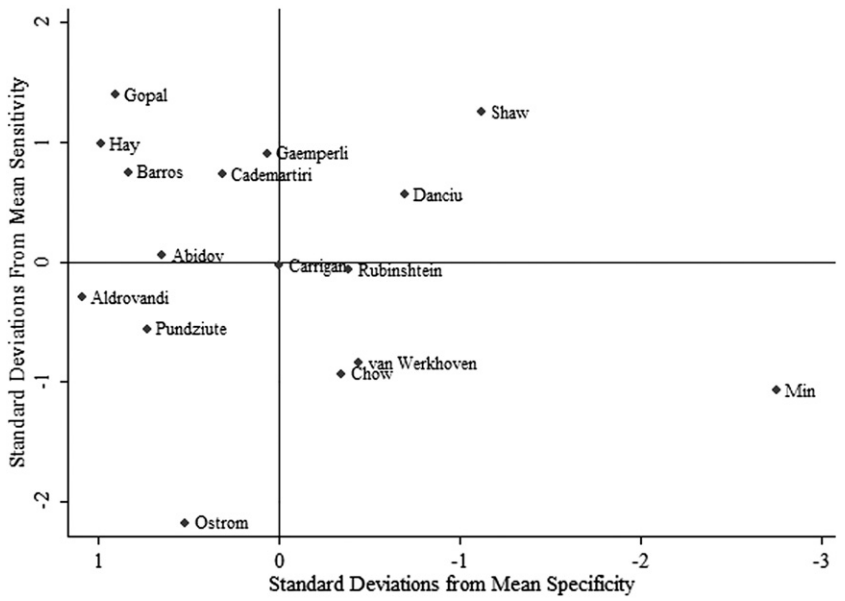

Figure 7 Graphical Assessment for Outliers for Sensitivity and Specificity

Two studies (Min et al. [16] and Ostrom et al. [18]) outlied for the end point of major adverse cardiac events comparing patients with cardiac computed tomography angiography showing nonobstructive coronary artery disease (CAD) with those showing obstructive CAD.

lished CAD, and duration of follow-up as a continuous variable (we annualized event rates to deal with differential follow-up). Last, it is important to re-emphasize that this analysis pooled studies of variable follow-up durations by converting to annualized event rates. This method is limited by its reliance on stable event rates, which is an imperfect assumption, although often used in prognostic studies. We evaluated for the effect of this assumption by performing sensitivity analyses by absolute event rates in addition to excluding studies with <12- or >24-month duration, but the overall effect sizes were not significantly different and were limited by greater heterogeneity. Of note, the overall length of follow-up of a median 20 months is relatively short. In the study with the longest follow-up duration by Ostrom et al. (18), CCTA became less able to discriminate events, suggesting that a "warranty period" exists on the duration of noninvasive prognostic studies (66). Long-term follow-up studies using 64-slice (or greater) MDCT are currently not available.

Study limitations. The study is limited by verification bias like many studies of noninvasive coronary risk stratification tests (67). In the 17 included studies, it was not always possible to separate coronary revascularization performed for acute coronary events from that performed for ongoing, chronic, stable chest pain referred for follow-up angiography based on CCTA findings. Hence, the observed increase in MACE is driven in part by coronary revascularization, demonstrating evidence of a workup or verification bias. That is, patients with CCTA evidence of a >50% stenosis are more likely to undergo catheterization and subsequent revascularization. This has been shown with other noninvasive assessments of CAD to decrease specificity, although the sensitivity may be unchanged or spuriously elevated. Hard events (death or MI) are less susceptible to verification bias and remained significantly predicted by degree of CAD seen on CCTA (Fig. 2), although the effect size and statistical power was diminished without including revascularization.

Despite the aforementioned limitations, our data clearly demonstrate that normal CCTA findings convey a very low risk of future death, MI, or coronary revascularization, at an annual event rate comparable to an otherwise healthy population. Furthermore, hard MACE and revascularization increased with increasing CAD from no disease to nonobstructive to severe disease. Considered in concert with the wealth of data regarding the high anatomic accuracy for CCTA (2), these results are convincing for CCTA to effectively diagnose CAD and convey risk strata for future adverse cardiovascular events.

Conclusions

Adverse cardiovascular events among patients with normal CCTA findings are very rare and comparable to a baseline risk among healthy patients. Increasing burden of CAD on CCTA is associated with an increasing rate of revascularization, MI, and death. However, for prediction of clinical events, the specificity and +LR are not useful for abnormal CCTA findings (as expected and consistent with other

noninvasive tests because many patients with disease will not have clinical events and, as such, are "test positive without events" in the context of this analysis). For predicting prognosis of adverse clinical events, the −LR of CCTA with normal findings is comparable to reported values for stress myocardial perfusion scan or stress echocardiography.

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REFERENCES

1. Moshage WE, Achenbach S, Seese B, Bachmann K, Kirchgeorg M. Coronary artery stenoses: three-dimensional imaging with electrocardiographically triggered, contrast agent-enhanced, electron-beam CT. Radiology 1995;196:707–14.
2. Mowatt G, Cook JA, Hillis GS, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. Heart 2008;94:1386–93.
3. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2010;56:1864–94.
4. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2009;3:190–204.
5. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 2009;3:122–36.
6. Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. J Am Coll Cardiol Img 2009;2:675–88.
7. Cademartiri F, Seitun S, Romano M, et al. Prognostic value of 64-slice coronary angiography in diabetes mellitus patients with known or suspected coronary artery disease compared with a nondiabetic population. Radiol Med 2008;113:627–43.
8. Carrigan TP, Nair D, Schoenhagen P, et al. Prognostic utility of 64-slice computed tomography in patients with suspected but no documented coronary artery disease. Eur Heart J 2009;30:362–71.
9. Choi EK, Choi SI, Rivera JJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. J Am Coll Cardiol 2008;52:357–65.
10. Fazel P, Peterman MA, Schussler JM. Three-year outcomes and cost analysis in patients receiving 64-slice computed tomographic coronary angiography for chest pain. Am J Cardiol 2009;104:498–500.
11. Gaemperli O, Valenta I, Schepis T, et al. Coronary 64-slice CT angiography predicts outcome in patients with known or suspected coronary artery disease. Eur Radiol 2008;18:1162–73.
12. Gopal A, Nasir K, Ahmadi N, et al. Cardiac computed tomographic angiography in an outpatient setting: an analysis of clinical outcomes over a 40-month period. J Cardiovasc Comput Tomogr 2009;3:90–5.
13. Hoffmann MH, Lessick J. Multidetector-row computed tomography for noninvasive coronary imaging. Expert Rev Cardiovasc Ther 2006;4:583–94.
14. Lesser JR, Flygenring B, Knickelbine T, et al. Clinical utility of coronary CT angiography: coronary stenosis detection and prognosis in ambulatory patients. Catheter Cardiovasc Interv 2007;69:64–72.
15. Matsumoto N, Sato Y, Yoda S, et al. Prognostic value of non-obstructive CT low-dense coronary artery plaques detected by multislice computed tomography. Circ J 2007;71:1898–903.
16. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol 2007;50:1161–70.
17. Noda M, Takagi A, Kuwatsuru R, Mitsuhashi N, Kasanuki H. Prognostic significance of multiple-detector computed tomography in conjunction with TIMI risk score for patients with non-ST elevation acute coronary syndrome. Heart Vessels 2008;23:161–6.
18. Ostrom MP, Gopal A, Ahmadi N, et al. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. J Am Coll Cardiol 2008;52:1335–43.
19. Rubinshtein R, Halon DA, Gaspar T, et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. Circulation 2007;115:1762–8.
20. Pundziute G, Schuijf JD, Jukema JW, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J Am Coll Cardiol 2007;49:62–70.
21. Shaw LJ, Berman DS, Hendel RC, Borges Neto S, Min JK, Callister TQ. Prognosis by coronary computed tomographic angiography: matched comparison with myocardial perfusion single-photon emission computed tomography. J Cardiovasc Comput Tomogr 2008;2:93–101.
22. van Werkhoven JM, Schuijf JD, Gaemperli O, et al. Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. J Am Coll Cardiol 2009;53:623–32.
23. Van Lingen R, Kakani N, Veitch A, Manghat NE, Roobottom CA, Morgan-Hughes GJ. Prognostic and accuracy data of multidetector CT coronary angiography in an established clinical service. Clin Radiol 2009;64:601–7.
24. Chow BJ, Wells GA, Chen L, et al. Prognostic value of 64-slice cardiac computed tomography severity of coronary artery disease, coronary atherosclerosis, and left ventricular ejection fraction. J Am Coll Cardiol 2010;55:1017–28.
25. Gilard M, Le Gal G, Cornily JC, et al. Midterm prognosis of patients with suspected coronary artery disease and normal multislice computed tomographic findings: a prospective management outcome study. Arch Intern Med 2007;167:1686–9.
26. Aldrovandi A, Maffei E, Palumbo A, et al. Prognostic value of computed tomography coronary angiography in patients with suspected coronary artery disease: a 24-month follow-up study. Eur Radiol 2009;19:1653–60.
27. Barros AJ, Blazquez MA, Leta R, Pujadas S, Alomar X, Pons-Llado G. [Noninvasive coronary angiography using multidetector computed tomography in patients with suspected coronary artery disease and a non-diagnostic exercise treadmill test result]. Med Clin (Barc) 2009;132:661–4.
28. Danciu SC, Herrera CJ, Stecy PJ, Carell E, Saltiel F, Hines JL. Usefulness of multislice computed tomographic coronary angiography to identify patients with abnormal myocardial perfusion stress in whom diagnostic catheterization may be safely avoided. Am J Cardiol 2007;100:1605–8.
29. Abidov A, Gallagher MJ, Chinnaiyan KM, Mehta LS, Wegner JH, Raff GL. Clinical effectiveness of coronary computed tomographic angiography in the triage of patients to cardiac catheterization and revascularization after inconclusive stress testing: results of a 2-year prospective trial. J Nucl Cardiol 2009;16:701–13.
30. Hay CS, Morse RJ, Morgan-Hughes GJ, Gosling O, Shaw SR, Roobottom CA. Prognostic value of coronary multidetector CT angiography in patients with an intermediate probability of significant coronary heart disease. Br J Radiol 2010;83:327–30.
31. Mark DB, Berman DS, Budoff MJ, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55:2663–99.
32. Mark DB, Kong DF. Cardiac computed tomographic angiography what's the prognosis? J Am Coll Cardiol 2010;55:1029–31.

33. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
34. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339: b2700.
35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
36. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed November 1, 2008.
37. Harbord R, Whiting P. Metandi: meta-analysis of diagnostic accuracy using hierarchical logistic regression. Stata J 2009;9:211–29.
38. Fagan TJ. Letter: Nomogram for Bayes theorem. N Engl J Med 1975;293:257.
39. Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Stat Med 2002;21:1525–37.
40. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882–93.
41. Adams GL, Trimble MA, Brosnan RB, et al. Evaluation of combined cardiac positron emission tomography and coronary computed tomography angiography for the detection of coronary artery disease. Nucl Med Commun 2008;29:593–8.
42. Bonello L, Armero S, Jacquier A, et al. Non-invasive coronary angiography for patients with acute atypical chest pain discharged after negative screening including maximal negative treadmill stress test. A prospective study. Int J Cardiol 2009;134:140–3.
43. Brook RD, Bard RL, Patel S, et al. A negative carotid plaque area test is superior to other noninvasive atherosclerosis studies for reducing the likelihood of having underlying significant coronary artery disease. Arterioscler Thromb Vasc Biol 2006;26:656–62.
44. Budoff MJ, Gopal A, Gul KM, Mao SS, Fischer H, Oudiz RJ. Prevalence of obstructive coronary artery disease in an outpatient cardiac CT angiography environment. Int J Cardiol 2008;129:32–6.
45. Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol 1996;27:285–90.
46. Fallavollita JA, Kumar K, Brody AS, Bunnell IL, Canty JM Jr. Detection of coronary artery calcium to differentiate patients with early coronary atherosclerosis from luminally normal arteries. Am J Cardiol 1996;78:1281–4.
47. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. J Am Coll Cardiol 2007;49:863–71.
48. Hadamitzky M, Freissmuth B, Meyer T, et al. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. J Am Coll Cardiol Img 2009;2:404–11.
49. Hines JL, Danciu SC, Shah M, Borg MJ, Biga C. Use of multidetector computed tomography after mildly abnormal myocardial perfusion stress testing in a large single-specialty cardiology practice. J Cardiovasc Comput Tomogr 2008;2:372–8.
50. Hoffmann U, Bamberg F, Chae CU, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. J Am Coll Cardiol 2009;53: 1642–50.
51. Hollander JE, Chang AM, Shofer FS, et al. One-year outcomes following coronary computerized tomographic angiography for evaluation of emergency department patients with potential acute coronary syndrome. Acad Emerg Med 2009;16:693–8.
52. Johnson TR, Nikolaou K, Fink C, et al. [Dual-source CT in chest pain diagnosis]. Radiologe 2007;47:301–9.
53. Keelan PC, Bielak LF, Ashai K, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation 2001; 104:412–7.
54. Menon M, Lesser JR, Hara H, et al. Multidetector CT coronary angiography for patient triage to invasive coronary angiography: performance and cost in ambulatory patients with equivocal or suspected inaccurate noninvasive stress tests. Catheter Cardiovasc Interv 2009;73:497–502.
55. Nicol ED, Stirrup J, Reyes E, et al. Sixty-four-slice computed tomography coronary angiography compared with myocardial perfusion scintigraphy for the diagnosis of functionally significant coronary stenoses in patients with a low to intermediate likelihood of coronary artery disease. J Nucl Cardiol 2008;15:311–8.
56. Walsh K, Chang AM, Perrone J, et al. Coronary computerized tomography angiography for rapid discharge of low-risk patients with cocaine-associated chest pain. J Med Toxicol 2009;5:111–9.
57. Hachamovitch R, Johnson JR, Hlatky MA, et al. The study of myocardial perfusion and coronary anatomy imaging roles in CAD (SPARC): design, rationale, and baseline patient characteristics of a prospective, multicenter observational registry comparing PET, SPECT, and CTA for resource utilization and clinical outcomes. J Nucl Cardiol 2009;16:935–48.
58. Schuijf JD, Mollet NR, Cademartiri F, et al. Do risk factors influence the diagnostic accuracy of noninvasive coronary angiography with multislice computed tomography? J Nucl Cardiol 2006;13:635–41.
59. Hamon M, Biondi-Zoccai GG, Malagutti P, Agostoni P, Morello R, Valgimigli M. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. J Am Coll Cardiol 2006;48:1896–910.
60. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
61. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 2007;49:227–37.
62. Motoyama S, Kondo T, Anno H, et al. Atherosclerotic plaque characterization by 0.5-mm-slice multislice computed tomographic imaging. Circ J 2007;71:363–6.
63. Vanhoenacker PK, Heijenbrok-Kal MH, Van Heste R, et al. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. Radiology 2007;244:419–28.
64. Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. Ann Intern Med 2010;152: 167–77.
65. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. Ann Intern Med 2008;149:889–97.
66. Min JK, Lin FY, Gidseg DS, et al. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: what is the "warranty period" for remaining normal? J Am Coll Cardiol 2010;55:1110–7.
67. Bielak LF, Rumberger JA, Sheedy PF 2nd, Schwartz RS, Peyser PA. Probabilistic model for prediction of angiographically defined obstructive coronary artery disease using electron beam computed tomography calcium score strata. Circulation 2000;102:380–5.

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